Specifically, at the time that this application was filed, one skilled in the art of peptide synthesis would understand that the R-group side chain of the amino acid Glycine is a hydrogen atom. See, for example, Figs. 5-2 and 5-6 of Lehninger et al.; *Principles of Biochemistry, Second Edition*; Chapter 5 Amino Acids; Worth Publishers, Inc.; New York, NY; 1993; pp. 112 and 115 (copies attached). See also Panel 2-5 of Alberts et al.; *Molecular Biology of the Cell, Third Edition*; Garland Publishing, Inc.; New York, NY; 1994; pp. 56-57 (copy attached). See also the definition of amino acids of Coombs; *Dictionary of Biotechnology, Second Edition*; Stockton Press; New York, NY; 1992; p. 19 (copy attached). Thus, it would be clear to one skilled in the art that R2 of formulae I and II of claim 4 can be a hydrogen atom and an amino acid side chain.

For at least these reasons, claim 4 satisfies the requirements of 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

II. Restriction Requirement

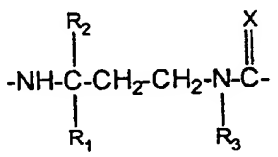
The Office Action makes the Restriction Requirement Final, and argues that the multiple individual compounds encompassed by formulae I and II cannot be a single special technical feature. Applicants respectfully assert that the Office Action misinterprets the PCT Unity of Invention Requirements, and applies the wrong standard in determining whether Unity of Invention exists between claims 1-18.

MPEP §1893.03(d) states that a group of inventions is considered linked to form a single inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature. MPEP §1893.03(d) further states that the expression special technical feature is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art.

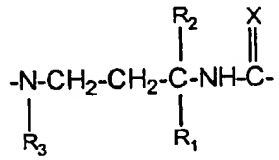
Under MPEP §1893.03(d), Unity of Invention exists between claims 1-18 where claims 1-18 are linked to form a single inventive concept. Claims 1-18 are linked to form a single inventive concept where claims 1-18 share a special technical feature, that is, where claims 1-18 share technical features that define the contribution that the claims as a whole make over the prior art.

All of claims 1-18 share the novel features of formulae I and II. Specifically, claim 1 recites the limitation:

> at least one unit chosen from the B units of general formulae (I) and/or (II):



(I)



(II)

> in which: R_1, R_2 and R_3 each independently of one another represent an amino acids side chain and may be identical or different, and X represents an oxygen or sulfur atom.

All of claims 2-18 ultimately depend from claim 1, and thus also include this feature.

As indicated in the Office Action, claim 1 is allowed and this novel feature is not taught by the prior art. Because this novel feature defines a contribution that the claims as a whole make over the prior art, it is a special technical feature under MPEP §1893.03(d). Because claims 1-18 share this special technical feature, claims 1-18 are linked to form a single inventive concept under MPEP §1893.03(d). For these reasons, Unity of Invention exists between all of claims 1-18.

Because Unity of Invention exists between claims 1-18, the Restriction Requirement is improper and claims 12-17 should be rejoined to, and allowed with, claims 1-11 and 18. Reconsideration and withdrawal of the Restriction Requirement are respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1-18 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

William P. Berridge
Registration No. 30,024

Philip A. Caramanica, Jr.
Registration No. 51,528

WPB:PAC

Attachments:

Figs. 5-2 and 5-6 of Lehninger et al.; *Principles of Biochemistry, Second Edition*; Chapter 5 Amino Acids; Worth Publishers, Inc.; New York, NY; 1993; pp. 112 and 115.

Panel 2-5 of Alberts et al.; *Molecular Biology of the Cell, Third Edition*; Garland Publishing, Inc.; New York, NY; 1994; pp. 56-57.

Coombs; *Dictionary of Biotechnology, Second Edition*; Stockton Press; New York, NY; 1992; p. 19.

Date: June 30, 2005

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Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

Lehninger et al.; Principles of Biochemistry, Second Edition; Chapter 5 Amino Acids; Worth Publishing Inc.; New York, NY; 1993; p. 112.

Amino Acids

Proteins can be reduced to their constituent amino acids by a variety of methods, and the earliest studies of proteins naturally focused on the free amino acids derived from them. The first amino acid to be discovered in proteins was asparagine, in 1806. The last of the 20 to be found, threonine, was not identified until 1938. All the amino acids have trivial or common names, in some cases derived from the source from which they were first isolated. Asparagine was first found in asparagus, as one might guess; glutamate was found in wheat gluten; tyrosine was first isolated from cheese (thus its name is derived from the Greek *tyros,* "cheese"); and glycine (Greek *glykos,* "sweet") was so named because of its sweet taste.

Figure 5–2 General structure of the amino acids found in proteins. With the exception of the nature of the R group, this structure is common to all the α-amino acids. (Proline, because it is an imino acid, is an exceptional component of proteins.) The α carbon is shown in blue. R (in red) represents the R group or side chain, which is different in each amino acid. In all amino acids except glycine (shown for comparison) the α-carbon atom has four different substituent groups.

Amino Acids Have Common Structural Features

All of the 20 amino acids found in proteins have a carboxyl group and an amino group bonded to the same carbon atom (the α carbon) (Fig. 5–2). They differ from each other in their side chains, or R groups, which vary in structure, size, and electric charge, and influence the solubility of amino acids in water. When the R group contains additional carbons in a chain, they are designated β, γ, δ, ϵ, etc., proceeding out from the α carbon. The 20 amino acids of proteins are often referred to as the standard, primary, or normal amino acids, to distinguish them from amino acids within proteins that are modified after the proteins are synthesized, and from many other kinds of amino acids present in living organisms but not in proteins. The standard amino acids have been assigned three-letter abbreviations and one-letter symbols (Table 5–1), which are used as shorthand to indicate the composition and sequence of amino acids in proteins.

We note in Figure 5–2 that for all the standard amino acids except one (glycine) the α carbon is asymmetric, bonded to four different substituent groups: a carboxyl group, an amino group, an R group, and a hydrogen atom. The α-carbon atom is thus a **chiral center** (see Fig. 3–9). Because of the tetrahedral arrangement of the bonding orbitals around the α-carbon atom of amino acids, the four different substituent groups can occupy two different arrangements in space, which are nonsuperimposable mirror images of each other (Fig. 5–3). These two forms are called **enantiomers** or **stereoisomers** (see Fig. 3–9). All molecules with a chiral center are also **optically active**—i.e., they can rotate plane-polarized light, with the direction of the rotation differing for different stereoisomers.

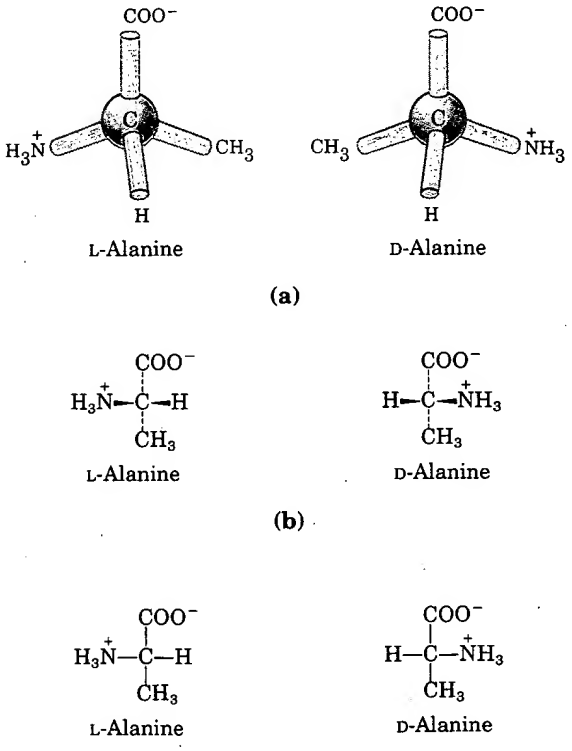


Figure 5–3 **(a)** The two stereoisomers of alanine. L- and D-alanine are nonsuperimposable mirror images of each other. **(b, c)** Two different conventions for showing the configurations in space of stereoisomers. In perspective formulas **(b)** the wedge-shaped bonds project out of the plane of the paper, the dashed bonds behind it. In projection formulas **(c)** the horizontal bonds are assumed to project out of the plane of the paper, the vertical bonds behind. However, projection formulas are often used casually without reference to stereochemical configuration.

Lehninger et al.; Principles of Biochemistry; Second Edition; Chapter 5 Amino Acids; Worth Publishers, Inc.; New York, NY; 1993; p. 115

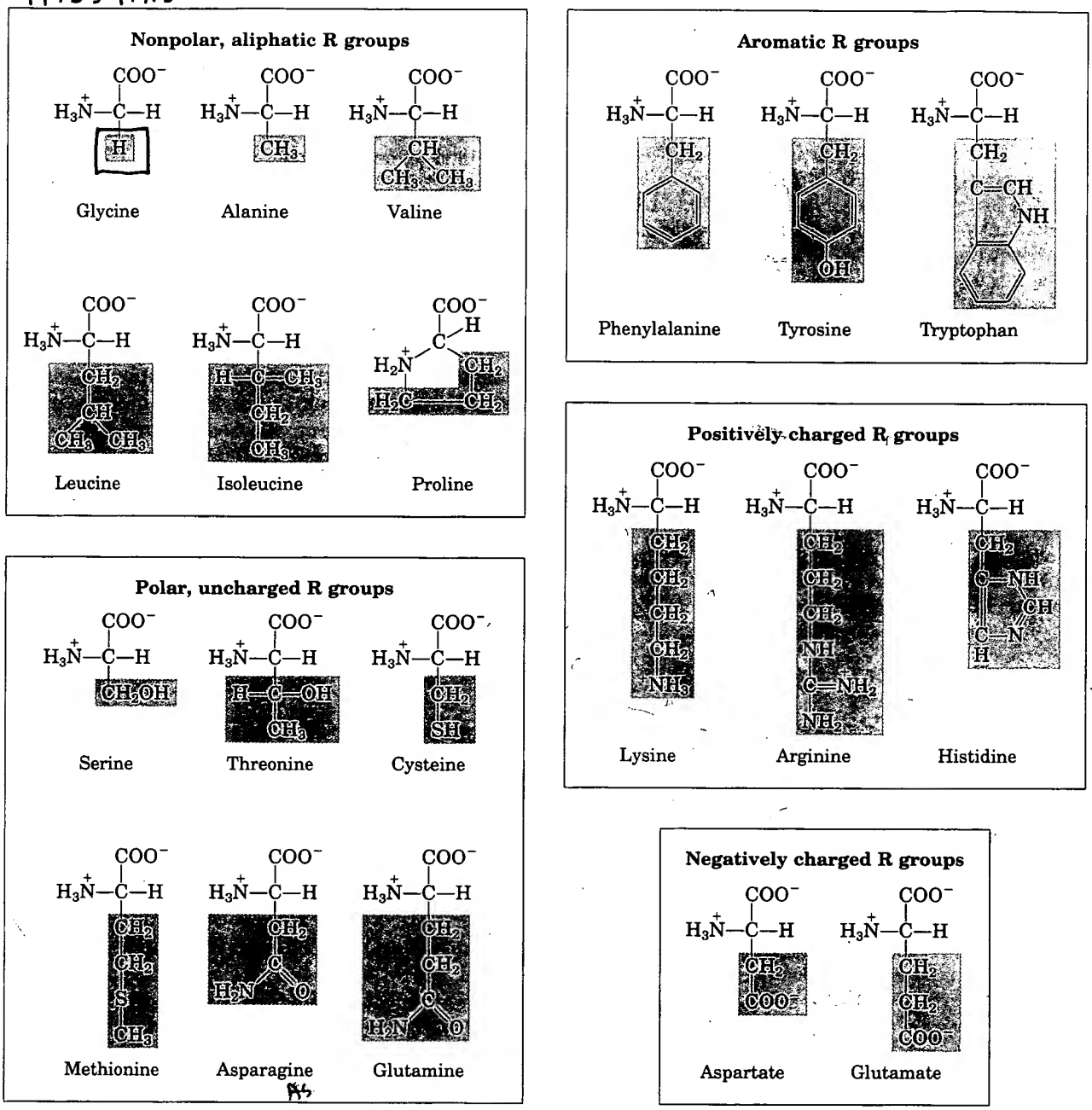


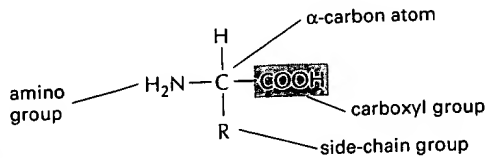
Figure 5–6 The 20 standard amino acids of proteins. They are shown with their amino and carboxyl groups ionized, as they would occur at pH 7.0. The portions in black are those common to all the amino acids; the portions shaded in red are the R groups.

Nonpolar, Aliphatic R Groups The hydrocarbon R groups in this class of amino acids are nonpolar and hydrophobic (Fig. 5–6). The bulky side chains of **alanine, valine, leucine,** and **isoleucine,** with their distinctive shapes, are important in promoting hydrophobic interactions within protein structures. **Glycine** has the simplest amino acid structure. Where it is present in a protein, the minimal steric hindrance of the glycine side chain allows much more structural flexibility than the other amino acids. **Proline** represents the opposite structural extreme. The secondary amino (imino) group is held in a rigid conformation that reduces the structural flexibility of the protein at that point.

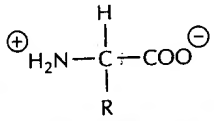
Alberts; MBOC, Third Edition; Garland Publishing, Inc.; New York, NY; 1994; pp 56-57
et al.

THE AMINO ACID

The general formula of an amino acid is

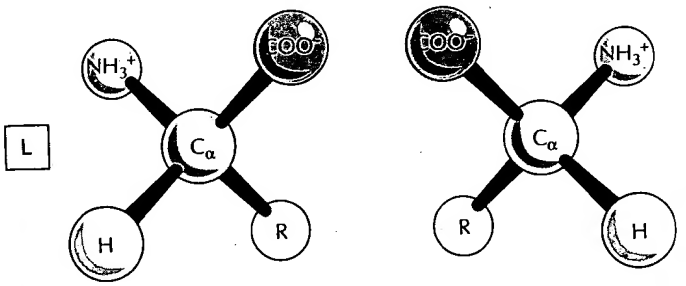


R is commonly one of 20 different side chains. At pH 7 both the amino and carboxyl groups are ionized.



OPTICAL ISOMERS

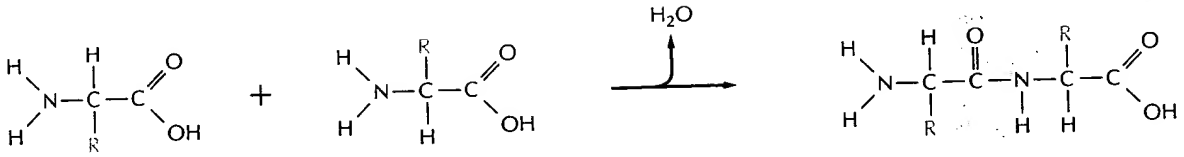
The α-carbon atom is asymmetric, which allows for two mirror image (or stereo-) isomers, D and L.



Proteins consist exclusively of L-amino acids.

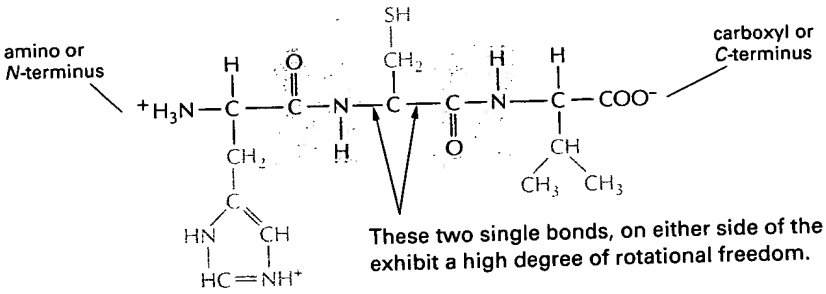
PEPTIDE BONDS

Amino acids are commonly joined together by an amide linkage, called a peptide bond.



peptide bond: The four atoms in each *gray box* form a rigid planar unit. There is no freedom of rotation about the C—N bond.

Proteins are long polymers of amino acids linked by peptide bonds, and they are always written with the *N*-terminus toward the left. The sequence of this tripeptide is His Cys Val.



These two single bonds, on either side of the rigid peptide unit, exhibit a high degree of rotational freedom.

FAMILIES OF AMINO ACIDS

The common amino acids are grouped according to whether their side chains are

- acidic
- basic
- uncharged polar
- nonpolar

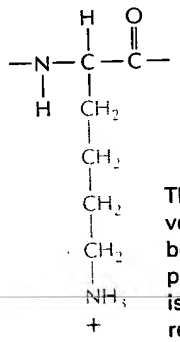
These 20 amino acids are given both three-letter and one-letter abbreviations.

Thus: alanine = Ala = A

BASIC SIDE CHAINS

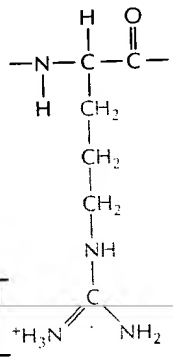
lysine

(Lys, or K)



arginine

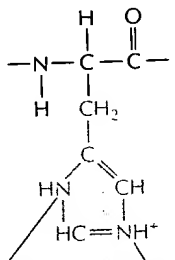
(Arg, or R)



This group is very basic because its positive charge is stabilized by resonance.

histidine

(His, or H)



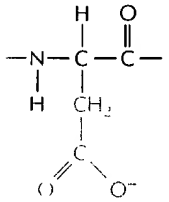
These nitrogens have a relatively weak affinity for an H^+ and are only partly positive at neutral pH.

Panel 2–5 The 20 amino acids involved in the synthesis of proteins.

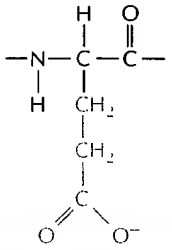
Alberts; MBOC, Third Edition; Garland Publishing, Inc.; New York, NY; 1994; pp 56-57 et al.

ACIDIC SIDE CHAINS

aspartic acid (Asp, or D)



glutamic acid (Glu, or E)



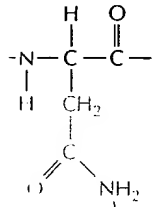
Amino acids with uncharged polar side chains are relatively hydrophilic and are usually on the outside of proteins, while the side chains on nonpolar amino acids tend to cluster together on the inside. Amino acids with basic or acidic side chains are very polar, and they are nearly always found on the outside of protein molecules.

The one letter code in alphabetical order:

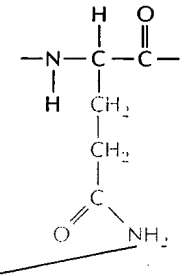
- Ala	G = Gly	M = Met	S = Ser
- Cys	H = His	N = Asn	T = Thr
- Asp	I = Ileu	P = Pro	V = Val
- Glu	K = Lys	Q = Gln	W = Trp
- Phe	L = Leu	R = Arg	Y = Tyr

UNCHARGED POLAR SIDE CHAINS

asparagine (Asn, or N)

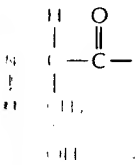


glutamine (Gln, or Q)

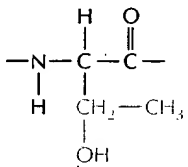


Although the amide N is not charged at neutral pH, it is polar.

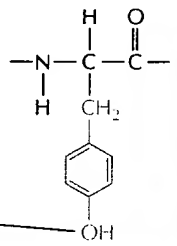
serine (Ser, or S)



threonine (Thr, or T)

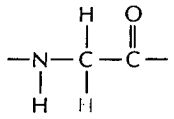


tyrosine (Tyr, or Y)



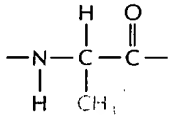
The OH group is polar.

NONPOLAR SIDE CHAINS

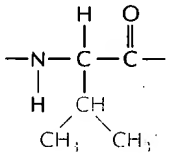


glycine (Gly, or G)

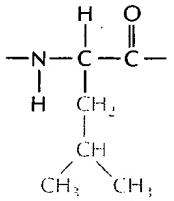
alanine (Ala, or A)



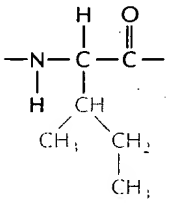
valine (Val, or V)



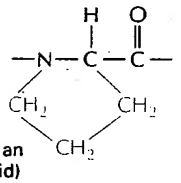
leucine (Leu, or L)



isoleucine (Ileu, or I)

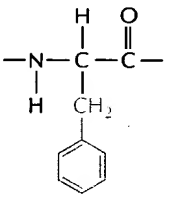


proline (Pro, or P)

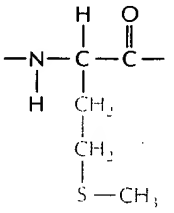


(actually an imino acid)

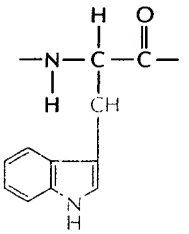
phenylalanine (Phe, or F)

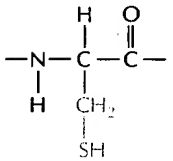


methionine (Met, or M)



tryptophan (Trp, or W)





cysteine (Cys, or C)

Paired cysteines allow disulfide bonds to form in proteins.

$$--CH_2-S-S-CH_2--$$

Coombs; Dictionary of Biotechnology, Second Edition; Stockton Press; New York, NY; 1992; p. 19.

5 amino acids per turn of the helix.
nation contributes to the secondary
ary structure of the protein.

terferon *See* leucocyte interferon.

ing double filter A wastewater
t process that consists of two bio-
ilters operating in series. Biomass
ates in the first filter as it consumes
the biochemical oxygen demand.
er of the filters is then reversed,
ie first filter becomes plugged with
, which results in the rapid autolysis
umption of the starved biomass.

ion of generations A situation in
e life cycle of an organism contains
erent types of organism that differ
, appearance and mode of repro-
These differences, usually reflect-
alternation between sexual and
generations, are common in plants
sitic animals. The sexual stage is
ie gametophyte generation and the
stage the sporophyte. In most
ie alternation of generations is as-
with alternations in diploid and
conditions and the intervention of
nd karyogamy. In some organisms
ycle may consist of more than two
ns which alternate regularly with
her.

A small sac such as occurs at the
of a bronchiole in the lungs or at
f a duct in some glands.

abbreviation used to denote an
utant.

in An immunomodulator produced
omyces.

nutation A class of suppressible
s that results in the creation of a
don in mRNA. This codon nor-
gnifies translation termination, so
ypeptide synthesis stops at the
ite. Such mutations can be sup-
n certain strains of *E. coli* possess-
NA with the AUC anticodon, and
hence inserting an amino acid at the UAG site and permitting continued translation.

American Type Culture Collection (ATCC) An organization holding a large collection of microorganisms and cell lines, including type specimens.

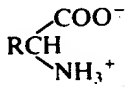
Ames test A test for potential mutagens and frameshift carcinogens. Compounds are screened for their ability to revert a series of known frameshift mutants in the hisD gene of *Salmonella typhimurium*. The reverted cells can be recognized since they will grow into colonies, which can be counted, on a medium that lacks histidine.

amide An organic compound obtained by replacing a hydroxyl group by an amino group.

amido black A chemical stain used to determine the position of proteins, including products of antigen/antibody interaction, on gels following chromatography or electrophoresis.

amino acid analyser An automated analytical device designed to separate and quantify individual amino acids from a complex mixture which may have been obtained from a protein hydrolysate or a physiological fluid. In general, the analyser consists of an automatic loading device to which a large number of samples can be added, a separation stage (usually based on a chromatographic procedure) and a detection system (based on a colourimetric or fluorometric assay technique). Early systems relied on two columns of ion exchange resins which were sequentially eluted with buffers of varying pH with the liquid stream from the columns passing through a colourimeter after having reacted with ninhydrin. The results were obtained as a trace in which peaks of different height or area indicated the presence of the various amino acids. These could be quantified by using standards to calibrate the machine. More recent machines are fully automated single-column liquid chromatographs, using microprocessors for control and calibration as well as calculation of the results which may be printed directly.

amino acids Chemical compounds of the following general formula



where R is a hydrogen atom (glycine) or any of a number of different organic groups. These compounds are zwitterions (dipolar ions). Most amino acids found in biological systems are present in the L-optical configuration. Amino acids are the basic building blocks of proteins, as well as participating in central metabolism and contributing to the synthesis of a variety of secondary products and biologically active molecules including co-enzymes, hormones and neurotransmitters. Several hundred different amino acids are known, but only 20 are normally found in proteins. These may be classified on the basis of similarity in structure or route of biosynthesis as shown in the table. Other biologically important amino acids include ornithine and citrulline which are intermediates of the urea cycle, Y-aminobutyric acid which functions as a neurotransmitter, β-alanine which is a precursor of pantothenic acid, and D-glutamate which is found in bacterial cell walls. Protein amino acids:

1. Hydrophobic
   Alanine
   Valine
   Leucine
   Isoleucine
   Proline (or hydroxyproline)
   Phenylalanine
   Tryptophan
   Methionine

2. Polar
   Glycine
   Serine
   Threonine
   Cysteine
   Tyrosine
   Asparagine
   Glutamine

3. Acidic
   Aspartic